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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
MYERS, CARLA J	
ART UNIT	**PAPER NUMBER**
1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/705,531	LU ET AL.	
	Examiner	Art Unit	
	Carla Myers	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 September 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-69* is/are pending in the application.

4a) Of the above claim(s) *2,7-46,48,49 and 52-69* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-6,47,50 and 51* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on September 28, 2007 has been entered.

2. Applicant's arguments and amendments to the claims have been fully considered but are not persuasive to overcome all grounds of rejection. All rejections not reiterated herein are hereby withdrawn. This action contains new grounds of rejection and is made non-final.

3. Claims 1-69 are pending.

Claims 1, 3-6, 47, 50 and 51 have been examined herein.

Claims 2, 7-46, 48, 49, and 52-69 are withdrawn from consideration as being drawn to an invention nonelected with traverse in the reply of May 22, 2006.

New / Modified Grounds of Rejections

Claim Rejections - 35 USC § 112 second paragraph

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 4, 5, 6, and 47 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 4 is indefinite over the recitation of "the DNA vector of claim 3" because this phrase lacks proper antecedent basis. While claim 4 previously refers to a vector the claim does not previously refer to a "DNA vector."

Claims 5 and 6 are indefinite over the recitation of "said polynucleotide molecule" because this phrase lacks proper antecedent basis.

Claim 47 is indefinite over the recitation of "said isolated PinX1 polynucleotide..." because this phrase lacks proper antecedent basis.

Claim Rejections - 35 USC § 112 – Written Description

5. Claims 1, 3-6, 47, 50 and 51 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

In analyzing the claims for compliance with the written description requirements of 35 U.S.C. 112, first paragraph, a determination is made as to whether the specification contains a written description sufficient to show they had possession of the full scope of their claimed invention at the time the application was filed.

The factors to be considered include disclosure of a complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, and any combination thereof.

Thereby, to ascertain whether the written description requirement is met for a genus claim, it is first determined whether a representative number of species have been described by their complete structure. It is then determined whether a representative number of species have been defined by other identifying characteristics.

In the present application, claims 1, 3-6 and 47 are drawn to PINX1 polynucleotides "comprising" the sequence of SEQ ID NO: 1 or 2. SEQ ID NO: 1 consists of the full length PINX1 cDNA of 1878 nucleotides. SEQ ID NO: 2 consists of 1036 nucleotides and encodes a portion of the C-terminal region of PINX1, including the C-terminal 74 amino acids of the PINX1 protein (SEQ ID NO: 3). In view of the "comprising" language, the claims encompass nucleic acids that contain the 1036 nucleotides of SEQ ID NO: 2 flanked at the 5' end by nucleotides of any length and identity. As such, to the extent that the claims encompass PINX1 polynucleotides comprising SEQ ID NO: 2, the claims define only a portion of PINX1 but do not define the complete structure of PINX1. Accordingly, the claims encompass a very large genus of splice variants, allelic variants, non-naturally occurring variants and homologues of PinX1

Claims 50 and 51 are drawn to pharmaceutical compositions comprising an antisense oligonucleotide fully complementary to "the mRNA sequence transcribed from a polynucleotide comprising SEQ ID NO: 1." The specification (para [0154] teaches that

an antisense oligonucleotide may consist of as few as 10bp or may comprise a full length cDNA. The claims define the mRNA in terms of the fact that it is transcribed from SEQ ID NO: 1. However, the claims do not define the complete structure of the mRNA. The claims thereby include antisense oligonucleotides fully complementary to both naturally occurring and non-naturally occurring mRNA, including potential splice variants and fragments, that may be transcribed from SEQ ID NO: 1.

The specification teaches the full length cDNA sequence of SEQ ID NO: 1, which encodes for PINX1. The specification teaches that PINX1 binds to Pin2/TFR1 (page 65) and binds to and inhibits telomerase (page 70). The specification also teaches a C-terminal domain of PINX1 (SEQ ID NO: 4) interacts with the telomerase catalytic subunit of hTERT and potentially inhibits its activity in vitro (page 28). SEQ ID NO: 2 consists of a fragment of 1036 of the 1878 nucleotides of SEQ ID NO: 1 and includes the sequence encoding the 75 amino acid sequence of SEQ ID NO: 4.

Regarding claims 50 and 51, the specification discloses full length mRNAs which consist of the RNA sequence of the cDNA of SEQ ID NO: 1. No additional fragments or splice variant mRNAs are disclosed. Presently, there are at least 4 known splice variants of PINX1 (see GeneCard for PINX1 available via url: < genecards.org/cgi-bin/carddisp.pl?gene=PINX1>). However, the specification does not disclosure any particular splice variants of SEQ ID NO: 1.

Accordingly, regarding claims 1, 3-6 and 47, the specification has adequately described in terms of their complete structure two nucleic acids - nucleic acids comprising SEQ ID NO: 1 and nucleic acids consisting of SEQ ID NO: 2. Regarding

claims 50 and 51, the specification has disclosed only one full length mRNA that is the mRNA sequence of the cDNA of SEQ ID NO: 1 (i.e., the mRNA that consists of SEQ ID NO: 1 with the exception that each thymine is replaced with a uracil).

No additional members of the claimed genus have been sufficiently described in terms of other relevant identifying characteristics . While claims 1, 3-6 and 47 recite that the PINX1 polynucleotide encodes for a polypeptide that binds to and inhibits telomerase, there is no clear disclosure in the specification as to the effect of adding additional amino acids to the N-terminal region of PINX1 will effect the tertiary structure of the protein and thereby its ability to bind to and inhibit telomerase. It is well known in the art that even a single conservative amino acid substitution can adversely effect the proper folding and biological activity of a protein if the amino acids are critical for functional activity. There is no clear disclosure in the specification of the effect of an amino acid substitution, deletion or addition on the activity of the proteins encoded by the claimed polynucleotides. Thereby, while the specification discloses that the polypeptide of SEQ ID NO: 4 binds to and inhibits hTERT, this information is not sufficient to fully characterize the structure-function relationship between all homologues, mutant variants, allelic variants and splice variants of PINX1 and telomerase binding activity.

It is also noted that possession may not be shown by merely describing how to obtain possession of members of the claimed genus or how to identify their common structural features. See University of Rochester, 358 F.3d at 927, 69 USPQ2d at 1895. Thereby, a showing of how to potentially identify and make other PINX1 polynucleotides

and mRNAs is not sufficient to establish that Applicant's were in possession of the invention as broadly claimed.

Again, the claimed genus is significantly large includes any PINX1 polynucleotide in which the 5' flanking region of up to 841 nucleotides. The claims also include any naturally occurring or non-naturally occurring mRNA (i.e., splice variant or fragment) that may be transcribed from SEQ ID NO: 1. Thus, the claims encompass naturally occurring and non-naturally occurring homologues, splice, deletion, insertion or substitution variants of PINX1. Yet, the specification teaches only the full length sequence of SEQ ID NO: 1 and a fragment thereof consisting of SEQ ID NO: 2. In the absence of a representative number of species of the claimed genus, there is insufficient descriptive support for the currently claimed genus of PINX1 polynucleotides and mRNAs.

The decisional law in this area has been very consistent. The Federal Circuit in Lilly, Fiers, Rochester and many other cases has determined that the written description issue applies to situations where the definition of the subject matter of the claims fails to provide description commensurate with the genus. The most recent case law directly supports this rejection. As the District Court in University of Rochester v. G.D. Searle & Co., Inc. (2003 WL 759719 W.D.N.Y.,2003. March 5, 2003.) noted "In effect, then, the '850 patent claims a method that cannot be practiced until one discovers a compound that was not in the possession of, or known to, the inventors themselves. Putting the claimed method into practice awaited someone actually discovering a necessary component of the invention." This is similar to the current situation since the breadth of

the current claims encompass PINX1 polynucleotides and mRNAs which the present inventors were not in the possession of, or which were not known to the inventors. As noted in Vas-Cath Inc. v. Mahurkar (19 USPQ2d 1111, CAFC 1991), the Federal Circuit concluded that:

"...applicant must also convey, with reasonable clarity to those skilled in art, that applicant, as of filing date sought, was in possession of invention, with invention being, for purposes of "written description" inquiry, whatever is presently claimed."

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision.

With respect to the present invention, there is no record or description which would demonstrate conception of any polynucleotides other than those expressly disclosed as comprising SEQ ID NO: 1 or consisting of SEQ ID NO: 2. Therefore, the claims fail to meet the written description requirement because the claims encompass a significantly large genus of polynucleotide sequences which are not described in the specification. Applicants attention is drawn to the Guidelines for the Examination of Patent Applications under 35 U.S.C. 112, ¶ 1 'Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001, and particularly Example 14 (http://www.uspto.gov/web/menu/written.pdf).

Response to Remarks:

In the response, Applicants traverse this rejection. Regarding claims 50 and 51, Applicants state that one of skill in the art would not doubt that Applicants were in possession of a sequence fully complementary to the mRNA sequence that results from the transcription of SEQ ID NO: 1, since the full and complete structure of such a

sequence can be envisioned based on an understanding of basic nucleic acid base pairing rules. This argument has been fully considered but is not persuasive. The claims are not in fact limited to antisense oligonucleotides that are defined in terms of their complete structure. In particular, the claims do not define the mRNA as being identical to SEQ ID NO: 1 with the exception that it includes uracil in place of thymine. Rather, the mRNA is defined in terms of being transcribed from a polynucleotide comprising. Such mRNAs include naturally occurring or artificially derived splice variants of the cDNA of SEQ ID NO: 1. Thereby, the disclosure of one full length mRNA that differs from SEQ I D NO: 1 in that it contains uracil in place of thymine is not sufficient to establish possession of the claimed genus of any mRNA that may be naturally or artificially transcribed from a sequence comprising SEQ ID NO: 1.

Regarding claims 1, 3-6 and 47, the response states that the claims have been amended to recite that the polypeptide encoded by PINX1 binds to and inhibits telomerase. Applicants assert that the claims therefore do not include variants of SEQ ID NO: 1, but include only sequences comprising SEQ ID NO: 2 that have the function of binding to and inhibiting telomerase. This argument has also been fully considered but is not persuasive. While the claims define the polynucleotides in terms of the function of the protein that it encodes, the claims do not define the complete overall structure of the genus of polynucleotides or define the genus of polynucleotides in terms of other relevant structural properties. As discussed above, the claims define 1036 nucleotides of a polynucleotide that potentially includes an additional 842 nucleotides. The identity and length of nucleotides flanking the 1036 nucleotides are not described.

As such, the claims encompass homologues, and naturally occurring and non-naturally occurring splice variants, isoforms and mutants and allelic variants of PINX1. However, the disclosure in the specification of a polynucleotide comprising the full length cDNA of SEQ ID NO: 1 and polynucleotides consisting of SEQ ID NO: 2 is not sufficient to establish possession of a representative number of the homologues, and naturally occurring and non-naturally occurring splice variants, isoforms and mutants and allelic variants of PINX1 encompassed by the claims. Therefore, the rejection is maintained.

Claim Rejections - 35 USC § 112 - Enablement

6. Claims 1, 3-6, 47, 50 and 51 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for isolated polynucleotides comprising SEQ ID NO: 1 and isolated polynucleotides consisting of SEQ ID NO: 2, does not reasonably provide enablement for polynucleotides comprising SEQ ID NO: 2 or antisense polynucleotides fully complementary to any mRNA transcribed from SEQ ID NO: 1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The following factors have been considered in formulating this rejection (*In re Wands,* 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

Breadth of the Claims:

Claims 1, 3-6 and 47 are drawn to PINX1 polynucleotides "comprising" the sequence of SEQ ID NO: 1 or 2. SEQ ID NO: 1 consists of the full length PINX1 cDNA of 1878 nucleotides. SEQ ID NO: 2 consists of 1036 nucleotides and encodes a portion of the C-terminal region of PINX1, including the C-terminal 74 amino acids of the PINX1 protein (SEQ ID NO: 3). In view of the "comprising" language, the claims encompass nucleic acids that contain the 1036 nucleotides of SEQ ID NO: 2 flanked at the 5' end by nucleotides of any length and identity. As such, to the extent that the claims encompass PINX1 polynucleotides comprising SEQ ID NO: 2, the claims define only a portion of PINX1 but do not define the complete structure of PINX1. Accordingly, the claims encompass a very large genus of splice variants, allelic variants, non-naturally occurring variants and homologues of PinX1.

Claims 50 and 51 are drawn to pharmaceutical compositions comprising an antisense oligonucleotide fully complementary to "the mRNA sequence transcribed from a polynucleotide comprising SEQ ID NO: 1." The specification (para [0154]) teaches that an antisense oligonucleotide may consist of as few as 10bp or may comprise a full length cDNA. The claims define the mRNA in terms of the fact that it is transcribed from SEQ ID NO: 1. However, the claims do not define the complete structure of the mRNA. The claims thereby include antisense oligonucleotides fully complementary to both naturally occurring and non-naturally occurring mRNA, including potential splice variants and fragments, that may be transcribed from SEQ ID NO: 1.

Further, claim 4 is drawn to a host cell comprising a DNA vector comprising a polynucleotide comprising SEQ ID NO: 1 or 2. The claim does not recite that the host cell is isolated. Accordingly, the claim reads on host cells present in vivo in a human or other organism produced by the in vivo delivery of a cell or vector.

Nature of the Invention:

The claims are drawn to polynucleotides comprising SEQ ID NO: 1 or 2 or fragments thereof. The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F. 3d 1316, 1330 (Fed Cir. 2001).

Teachings in the Specification and State of the Art:

The specification teaches the full length cDNA sequence of SEQ ID NO: 1, which encodes for PINX1. The specification teaches that PINX1 binds to Pin2/TFR1 (page 65) and binds to and inhibits telomerase (page 70). The specification also teaches a C-terminal domain of PINX1 (SEQ ID NO: 4) interacts with the telomerase catalytic subunit of hTERT and potentially inhibits its activity in vitro (page 28). SEQ ID NO: 2 consists of a fragment of 1036 of the 1878 nucleotides of SEQ ID NO: 1 and includes the sequence encoding the 75 amino acid sequence of SEQ ID NO: 4.

Regarding claims 50 and 51, the specification discloses full length mRNAs which consist of the RNA sequence of the cDNA of SEQ ID NO: 1. No additional fragments or splice variant mRNAs are disclosed. Presently, there are at least 4 known splice variants of PINX1 (see GeneCard for PINX1 available via url: < genecards.org/cgi-

bin/carddisp.pl?gene=PINX1>). However, the specification does not disclosure any particular splice variants of SEQ ID NO: 1.

The Predictability or Unpredictability of the Art and Degree of Experimentation:

The claims encompass polynucleotides in which only the 3' region encoding the C-terminal region of the polypeptide are defined. The sequences at the 5' terminus of the polynucleotide are not defined. However, the complete structure of a polypeptide determines its binding and inhibitory activity, rather than isolated regions of the polypeptide. Yet, there is no clear disclosure in the specification as to the effect of adding additional amino acids to the N-terminal region of PINX1 will effect the tertiary structure of the protein and thereby its ability to bind to and inhibit telomerase. It is well known in the art that even a single conservative amino acid substitution can adversely effect the proper folding and biological activity of a protein if the amino acids are critical for functional activity. There is no clear disclosure in the specification of the effect of an amino acid substitution, deletion or addition in the N-terminal region on the activity of the proteins encoded by the claimed polynucleotides. While the specification discloses that the polypeptide of SEQ ID NO: 4 binds to and inhibits hTERT, this information is not sufficient to fully characterize the structure-function relationship between all homologues, mutant variants, allelic variants and splice variants of PINX1 and telomerase binding activity. Thereby, it is highly unpredictable as to how the addition of any number of nucleotides of any identity to the 5' region of SEQ ID NO: 2will effect the overall functional properties of the resulting gene and thus the polypeptide encoded thereby.

It is also unpredictable as to what would be the overall structure of a mRNAs in the genus of mRNAs transcribed from SEQ ID NO: 1. As discussed above, the claims encompass both naturally occurring and artificially generated mRNA splice variants of SEQ ID NO: 1. At present at least 4 splice variants of PINX1 are known. However, the specification does not disclose the existence of such mRNA splice variants or any other splice variants of SEQ ID NO: 1. It is thus highly unpredictable as to what would be the overall structure and function of mRNA splice variants naturally or artificially transcribed from SEQ ID NO: 1.

Regarding claim 4, the specification (para [0034] of the PG pub) states gene sequences may be cloned into a vector for the purposes of gene therapy. It is stated that retroviral vectors are known which can be used for gene therapy (para [0327]). It is also stated that gene therapy can be a direct in vivo process where genetic material is transferred to cells in a desired region of a patient's body or genetic material may be transferred into cells which are implanted into a patient. It is acknowledged that biologically functional viral and plasmid DNA vectors capable of expression and replication in a host are known in the art. Such vectors are used to incorporate DNA sequences of the invention. However, the instant specification does not teach how to overcome problems with in vivo delivery and expression with respect to the administration of the claimed nucleic acids or viral vectors comprising said nucleic acids. The state of the art as of the priority date sought for the instant application is that in vivo gene delivery is not well developed and is highly unpredictable. For instance Verma et al., (Nature, 1997, Vol. 389, pp. 239-242) teach that the Achilles heel of gene

therapy is gene delivery. Verma et al state that the ongoing problem is the inability to deliver genes efficiently and to obtain sustained expression (page 239, column 3). Even as of 2003, those of skill in the art recognize the hurdles remaining in the development of gene therapy protocols. As of the priority date sought, it was well known in the art how to infect or transfect cells in vitro or ex vivo with viral vectors. However, using viral vectors to deliver DNA to an organism in vivo, or using infected or transfected cells to deliver nucleic acids which encode a particular protein sequence to an organism in vivo is in the realm of gene therapy, and as of the priority date sought, highly unpredictable in view of the complexity of in vivo systems. Orkin et al.("Report and Recommendation of the Panel to Assess the NIH Investment in Research on Gene Therapy", NIH, 1995) state that as of 1995, clinical efficacy had not been definitively demonstrated with any gene therapy protocol (page 1, second paragraph). Orkin et al., defines gene therapy as the transfer of DNA into recipient cells either ex vivo or in vivo (page 7, under the heading "Gene transfer"), thus encompassing the instant claims drawn to the administration of antigen presenting cells transfected or infected ex vivo. Orkin et al., concludes that, "none of the available vector systems is entirely satisfactory, and many of the perceived advantages of vector systems have not been experimentally validated. Until progress is made in thee areas, slow and erratic success in applying gene transfer methods to patients can be expected." Orkin et al. comment that direct administration of DNA or DNA in liposomes is not well developed and hindered by the low efficiency of gene transfer (page 8, paragraph 5). Orkin et al. teach that adequate expression of the transferred genes is essential for therapy, but that current data regarding the level and

consistency of expression of transferred genes in animal models was unknown. Orkin et al states that in protocols not involving ex vivo infections/transfection, it is necessary to target the expression of the transferred genes to the appropriate tissue or cell type by means of regulatory sequences in gene transfer vectors. Thomas (Nature. 2003. 4: 346-358) teaches that "(a)s more work is needed to develop site-specific integrating vectors, more work is also needed to improve the ability of vectors to home in on and infect specific target-cell populations." The specification does not, however, teach a vector having a specific regulatory sequence, which would direct the expression of the nucleic acids within the appropriate tissue type. The specification does not remedy any of the deficiencies in the prior art with regard to gene therapy. Given the lack of any guidance from the specification on how to overcome the above issues pointed out by Orkin, Verma, and Thomas, undue experimentation would be required to make and use the host cells present in vivo, as encompassed by the claims. It is noted that amendment of claim 4 to recite "an isolated host cell comprising .... " would overcome this aspect of the rejection.

Amount of Direction or Guidance Provided by the Specification:

The specification does not provide any specific guidance as to how to predictably make and use nucleic acids comprising SEQ ID NO: 2 flanked by nucleotides of any length and identity. While one could generate a significantly large genus of nucleic acids in which nucleotides of any identity are added to the 5' or 3' terminus of SEQ ID NO: 2 and then assay each of these nucleic acids to try to determine their biological activity, such trial-by-error experimentation is considered to be undue. Providing

methods for searching for additional nucleic acids and trying to determine the function of the resulting nucleic acid or trying to establish an association between the nucleic acids and binding to and inhibiting telomerase is not equivalent to teaching how to make and use specific nucleic acids.

Similarly, insufficient guidance is provided in the specification as to how to make and use a representative number of alternatively spliced variants of SEQ ID NO: 1, and the antisense oligonucleotides fully complementary thereto.

Working Examples:

Again, the specification teaches only a full length cDNA comprising SEQ ID NO: 1 and one fragment thereof – i.e. a polynucleotide consisting of SEQ ID NO: 2, wherein said polynucleotide encodes for a polypeptide which binds Pin2/TRF-1 and telomerase. The specification does not provide any working examples of how to predictably make and use nucleic acids comprising SEQ ID NO: 2 and including additional nucleotides of any length and identity. Further, the specification exemplifies a single mRNA that differs from SEQ ID NO: 1 in that it contains uracil in place of thymine. No additional naturally or non-naturally occurring splice variants of PINX1 mRNAs have been disclosed. Thus, specific working examples are not provided in the specification for a representative number of homologues, splice variants, mutants or allelic variants of PinX1.

Conclusions:

Case law has established that "(t)o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *In re Wright* 990 F.2d 1557, 1561. *In re*

Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) it was determined that "(t)he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art". The amount of guidance needed to enable the invention is related to the amount of knowledge in the art as well as the predictability in the art. Furthermore, the Court in *Genetech Inc. v Novo Nordisk* 42 USPQ2d 1001 held that "(I)t is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of the invention in order to constitute adequate enablement". In the instant case, the claims do not bear a reasonable correlation to the scope of enablement because the specification teaches only SEQ ID NO: 1 and a fragment thereof consisting of SEQ ID NO: 2, whereas the claims encompass a significantly large genus of nucleic acids, in which the overall structural properties and functional properties (with respect to claims 50 and 51) of the nucleic acids are not defined. As set forth above, in view of the unpredictability in the art, extensive experimentation would be required to make and use the broadly claimed genus of homologues, mutant, allelic and splice variants of PINX1. Accordingly, although the level of skill in the art of molecular biology is high, given the lack of disclosure in the specification and in the prior art, it would require undue experimentation for one of skill in the art to make and use the broadly claimed invention.

Response to Remarks:

In the response, Applicants state that the fact that the claims do not define the 5' nucleotides of the sequences that flank SEQ ID NO: 2 does not render the claims non-enabled. Applicants assert that adding nucleotides to the sequence of SEQ ID NO: 2

and determining the effect of the nucleotides on the ability of an encoded protein to bind to and inhibit telomerase is routine. It is stated that undue experimentation is not required to generate and assay for such polynucleotides because the specification provides assays for detecting telomerase binding and inhibition. Applicants arguments have been fully considered but are not persuasive. The present claims are not directed to a method of screening for polynucleotides encoding polypeptides that bind to and inhibit telomerase. Rather, the present claims are directed to the polynucleotides themselves which encode for a polypeptide that binds to and inhibits telomerase. While methods are known in the art for synthesizing nucleic acids, modifying the sequence of nucleic acids and for determining if a polypeptide binds to and inhibits telomerase activity, the outcomes of such methodology cannot be predicted. It remains unpredictable as to how the addition of nucleotides to the 5' terminus of SEQ ID NO: 2 will alter the functional properties of an encoded protein. As discussed above, even a single amino acid substitution can effect the secondary and tertiary structure of a protein and thus its ability to bind to and inhibit telomerase. However, the specification does not provide any specific guidance as to how many nucleotides and the identity of such nucleotides which may be added to the 5' terminus of SEQ ID NO: 2 without altering the ability of an encoded protein to bind to and inhibit telomerase. In the absence of specific guidance and in view of the unpredictability in the art, it is maintained that undue experimentation would be required to make and use a representative number of homologues, splice variants, mutant and allelic variants encompassed by the claims. Further, claims 50 and 51 are drawn to antisense polynucleotides that are fully

complementary to any mRNA transcribed from SEQ ID NO: 1. The claims therefore include naturally occurring and artificially generated splice variants of SEQ ID NO: 1. However, the specification discloses only a full length mRNA that differs from the cDNA of SEQ ID NO: 1 in that includes uracil in place of thymine. There is no specific guidance provided in the specification as to what would be the identity of alternatively spliced variants of SEQ ID NO: 1 or how to predictably use antisense oligonucleotides complementary to said mRNAs. Accordingly, it is maintained that given the lack of disclosure in the specification of a representative number of naturally and non-naturally occurring splice variant mRNAs of SEQ ID NO: 1 and given the unpredictability of the art, it would require undue experimentation for one of skill in the art to make and use the invention as broadly claimed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is 571-272-0747. The examiner can normally be reached on Monday-Thursday (6:30-5:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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